REMARKS

Summary of the Office Action

Claims 6, 9-26, and 33 are pending in the application, of which claims 6 and 9-15 are under examination. Claims 16-26 and 33 are withdrawn from consideration as being drawn to a non-elected invention. Claims 6 and 11 have been amended to delete the phrase "which is derived from the hydrophobic portion of a signal peptide secreted from cells." Claims 6 and 11 have also been amended to recite that "the importation competent signal peptide comprises a hydrophobic portion of a naturally occurring signal peptide that mediates translocation of a protein across the endoplasmic reticulum (ER) membrane." Support for this amendment can be found throughout the specification, and specifically on page 2, lines 16-21. Support for "naturally occurring" can be found at least on page 3, lines 12-15. Claims 9 and 12 have been amended to recite "importation competent signal peptide." It is believed no new matter is added by this amendment.

Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 6 and 9-15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action first objects to the term "derived from the hydrophobic portion of a signal peptide" in the claims. Applicants have amended the claims to make it clear that the method uses naturally occurring hydrophobic portions of signal peptides that mediate translocation of a protein across the ER membrane. The Office Action also states that claims 9 and 12 potentially are drawn to two different signal peptides, and are therefore not enabled. While applicants respectfully disagree, the claims have been amended to clarify that claims 9 and 12 refer to the importation competent signal peptide.

The Office Action goes on to state that, "...even if the claims were limited to an importation competent signal peptide comprising the hydrophobic domain of a signal peptide of a protein secreted from cells, the claim scope would still exceed the enabled scope. Applicant's position remains rooted in the assumption that the hydrophobic portion of a signal peptide of a protein secreted from cells defines a signal peptide as 'importation competent'." In support of this argument, the Office Action then cites the background portion of the present application, and draws the conclusion that, "Thus, the specification teaches that what was known in the art was that translocation of most proteins across cellular membranes via a signal peptide dependent mechanism required a protein-conducting channel and speculates that some secretory proteins might cross cellular membranes directly through the lipid bilayer." (Page 6 of Office Action).

The logic of the rejection appears to be that (1) those of skill in the art prior to Applicants' invention believed that proteins and channels were required to mediate all passage of proteins through cell membranes, (2) the claimed signal peptides of secreted proteins do not include or provide the proteins and channels that allegedly would be required to allow importation of the claimed complexes, and (3) therefore Applicants allegedly have not enabled the claimed method of importation using the hydrophobic portions of naturally occurring signal peptides. The flaw in the reasoning of the rejection is that the hydrophobic portions of naturally occurring signal peptides that mediate translocation of a protein across the endoplasmic reticulum (ER) membrane do naturally possess structures that allow them to mediate importation into cells of attached proteins in the absence of special proteins and channels in the cell membrane. This is the core and the basis of Applicants' discovery underlying the claimed

method. Given this fact, there is no basis to allege that it would require undue experimentation to practice the claimed method.

Applicants are required to enable the practice of their invention, not correct every misconception contained in the prior art as the present rejection appears to require. Applicants have discovered that the hydrophobic portion of naturally occurring signal peptides naturally possess a structure that allows them to mediate importation into cells. The fact that the prior art believed that proteins and protein channels were always required for such importation does not negate or contradict Applicants' discovery. It is perfectly true that there are other mechanisms of cell importation that involve proteins and channels, but Applicants' method does not depend on them and whatever issues might need to be overcome or enabled to use such other importation mechanisms does not affect the basic simplicity of the mechanism of Applicants' claimed importation method. All that Applicants are required to enable is what Applicants are claiming. Because the hydrophobic portions of naturally occurring signal peptides that mediate translocation of a protein across the ER membrane naturally possess structures that allow importation into cells, which is Applicants' discovery, the burden of experimentation in practicing the claimed method is slight. In this case, there is no basis for holding that the claimed method lacks enablement.

The present rejection cannot be sustained even if it were the case that some hydrophobic portions of some naturally occurring signal peptides that mediate translocation of a protein across the ER membrane were not importation competent. This is because the claims are limited not only to the use of hydrophobic portions of naturally occurring signal peptides that mediate translocation of a protein across the ER membrane, but to those that allow the importation of the

claimed complex into cells. Thus, the claimed method excludes the use of hydrophobic portions of naturally occurring signal peptides that fail to allow the importation of the claimed complex into cells. It is submitted that it would not require undue experimentation to determine if such a hydrophobic portion does in fact allow the importation of the claimed complex into cells. A parallel example would be that applicants are claiming a car with a working motor, wherein the car has a trailer attached to it. The present rejection is akin to a rejection stating that such a claim is not enabled because not all cars have working motors. Applicants are not claiming that all cars have working motors, and are not therefore required to show that all cars have working motors. One of skill in the art would have been able to identify cars with working motors without the need of undue experimentation, just like the present case, where one of skill in the art could identify signal peptides that can mediate translocation across the ER membrane. The present claims to the use of naturally occurring hydrophobic portions of signal peptides that mediate translocation of proteins across the ER membrane is like pointing to a car lot and saying that one of skill in the art could identify cars with motors that are capable of running. That is not to say that all the cars in the lot have motors that can run, but that one of skill in the art could easily determine which cars have working motors, and then select those cars to attach to the trailer. Thus, there is no undue experimentation in practicing the method as claimed. Accordingly, for at least this reason, the present rejection cannot be maintained.

The Office Action cites US Patent 6,841,535, and asserts that this patent teaches two hydrophobic domains (Peps -1.4 and -2.1) which are not sufficient alone to transfect drugs, proteins, or peptides. The Office Action goes on to allege that the vague structural specifications disclosed in the instant application do not define a peptide as importation competent. However,

applicants are not claiming that any peptide can be importation competent. Claim 6, for example, is drawn to administering a complex comprising a peptide, polypeptide, or protein linked to an importation competent signal peptide comprising *the hydrophobic portion of a naturally occurring signal peptide that mediates translocation of a protein across the endoplasmic reticulum (ER) membrane*. The claim is not drawn to any hydrophobic portion of any peptide, but a naturally occurring hydrophobic portion of a *signal peptide that can mediate translocation across the ER*. Therefore, Applicants are not relying on the hydrophobic portion to defining the peptide as being capable of penetrating through cells. Instead, the hydrophobic portion is specifically from a signal peptide that has already been identified as one that is functional for mediating translocation of a protein across the ER. It is Applicants' discovery that such hydrophobic portions of naturally occurring signal peptides that mediate translocation across the ER membrane naturally possess a structure that allows importation into cells.

Specifically regarding US Patent 6,841,535, Applicants would like to point out that there are major differences between these two hydrophobic domains and those that are claimed. First of all, the hydrophobic domains mentioned in the '535 patent are not from signal sequences and are not naturally occurring. Instead, peptides -1.4 and -2.1 were designed *de novo* based on the concept of the patent that residues that are spaced a certain way, and have a given number of hydrophobic residues in given positions, are able to penetrate the cell. Thus, peptides -1.4 and -2.1 do not meet the limitations of the claims and do not provide any information that bears on the function or enablement of the claimed hydrophobic portions and method. For this reason, as well as those given above, applicants therefore respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 6-15 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description. Applicants respectfully traverse. However, in an effort to expedite prosecution, the claims have been amended to delete the phrase, "derived from the hydrophobic portion of a signal peptide."

The Office Action states that, "even if the claims had been limited to comprising the hydrophobic portion of a signal peptide of a protein secreted from cells, the art teaches that a hydrophobic portion alone does not define a peptide capable of penetrating through the cell membrane from outside the cell to the interior of the cell." Applicants respectfully traverse. The Office Action states that a hydrophobic portion alone does not define a peptide capable of penetrating through the cell membrane. However, this is not what applicants are claiming. Claim 6, for example, is drawn to administering a complex comprising a peptide, polypeptide, or protein linked to *a naturally occurring hydrophobic portion of a signal peptide that mediates translocation of a protein across the ER membrane.* The claim is not drawn to any hydrophobic portion of *any* peptide, but to a *naturally occurring hydrophobic portion of a signal peptide that mediates translocation of a protein across the ER membrane.*

The Written Description requirement requires that the specification lead those of skill in the art to conclude that the applicant had possession of the invention. The present rejection appears to be based on the following logic: (1) not all hydrophobic amino acid sequences will be importation competent, (2) the application allegedly does not provide structural description that distinguishes those hydrophobic amino acid sequences that will be importation competent form those that will not be importation competent, and (3) therefore the application allegedly does not provide a written description of the structure of those hydrophobic amino acid sequences that are

importation competent. This logic does not establish that the present claims lack sufficient written description in the specification. First, Applicants note that the claims are limited to the use of a naturally occurring hydrophobic portion of a signal peptide that mediates translocation of a protein across the ER membrane. Thus, the claims are limited to the use of naturally occurring hydrophobic portions of a signal peptide. Such hydrophobic portions are well known to those of skill in the art and their identifications and use is well established. For example, the SIGPEP database referred to in the specification and well known to those of skill in the art is a catalog of naturally occurring signal peptides (with naturally occurring hydrophobic portions). Applicants submit that naturally occurring hydrophobic portions of signal peptides that mediate translocation of a protein across the ER membrane are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. As established by the Federal Circuit in *Amgen Inc. v. Hoechst Marion Roussel, Inc and TKT.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003), such facts are sufficient to establish written description even though specific structural information is not known and not provided. In *Amgen*, the claims of Amgen's patents referred to types of cells that can be used to produce recombinant human EPO. TKT (Amgen's opponent) argued that, because the Amgen patents did not describe the structure of the claimed cells, the patents failed to provide adequate written description of the claimed subject matter as required by *Eli Lilly* and *Enzo*. The court in *Amgen* rejected this argument, holding that Amgen's claims, including the recited cells, were adequately described in Amgen's patents. The court noted that unlike in *Eli Lilly* or *Enzo* "the claim terms at issue here [in *Amgen*] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend....This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to

identify types of cells (instead of undescribed, previously unknown DNA sequences), the words 'vertebrate' and 'mammalian' readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identify of the members of the genus.'" Like the cells of *Amgen*, the claimed naturally occurring hydrophobic portions of signal peptides are well known biological materials; well classified and easily recognized by those of skill in the art. As a result, and as in *Amgen*, the present application satisfies the written description requirement for the present claims.

As discussed above, the Office Action cites US Patent 6,841,535, and asserts that this patent teaches two hydrophobic domains (Peps -1.4 and -2.1) which are not sufficient alone to transfect drugs, proteins, or peptides. The Office Action goes on to state that the presence of a hydrophobic domain alone is not enough to make a peptide importation competent, as evidenced by this patent. Applicants would like to point out that there are major differences between these two hydrophobic domains and those that are claimed. First of all, the hydrophobic domains mentioned in the '535 patent are not from signal sequences and are not naturally occurring. Instead, peptides -1.4 and -2.1 were designed *de novo* based on the concept of the patent that residues that are spaced a certain way, and have a given number of hydrophobic residues in given positions, are able to penetrate the cell. Thus, peptides -1.4 and -2.1 do not meet the limitations of the claims an do not provide any information that bears on the function or description of the claimed hydrophobic portions and method.

The Office Action states that the Federal Circuit has held that a patentee will not be deemed to have species sufficient to constitute the genus by virtue of having disclosed a single species when the evidence indicates ordinary artisans could not predict the operability in the

invention of any species other than the one described. Applicants first note that the "representative species" standard does not apply when the subject matter involved is well known and not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. As discussed above, the claimed use of naturally occurring hydrophobic portions of signal peptides that mediate translocation of proteins across the ER membrane are well known biological components. Once a signal peptide has been found, one of skill in the art can readily identify the hydrophobic portion. And again, applicants are not claiming the hydrophobic portion of any peptide, but rather the hydrophobic portion of signal peptides that mediate translocation of proteins across the ER membrane. Even if the "representative species" standard was relevant here, the examples presented in the application and with prior responses are representative of other naturally occurring hydrophobic portions of signal peptides that mediate translocation of proteins across the ER membrane. Such peptides are a well-known class of peptides and so those of skill in the art would readily agree that Applicants were in possession of this class of peptides. Applicants assert that is the case in the present invention, as one of skill in the art could readily and easily comprehend a naturally occurring hydrophobic portion of a signal peptide that can mediate translocation of a protein across the ER, based on the example given in the specification.

The Office Action uses the example of the V5 epitope tag, which has 50% hydrophobic residues, and is about 10 amino acids long. The Office Action then asserts that this peptide would read on the claimed invention. This is not the case. As pointed out, applicants are not claiming any peptide with a hydrophobic region. Applicants are claiming a naturally occurring hydrophobic portion of a signal peptide that mediates translocation of a protein across the ER

membrane. The V5 epitope tag is not a signal sequence and thus is not relevant to the present claims.

The Office Action then discusses the mechanism of translocation across the ER membrane, and states that this would not correlate with translocation from outside the cell to the interior of the cell. The Office Action goes on to allege that based on this teaching, neither the prior art nor the instant specification discloses the relevant identifying characteristics of the "importation competent signal peptide" of the claims. Applicants traverse this for the following reasons. The present claims make use of naturally occurring hydrophobic portions of signal peptides that mediate translocation across the ER membrane. Such naturally occurring hydrophobic portions are known and do not require further description for the reasons discussed above. For this reason, as well as the reasons given above, applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 9 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant considers to be his invention. Applicants respectfully traverse. However, in an effort to expedite prosecution, claims 9 and 12 have been amended to recite "importation competent signal peptide." It is submitted that this clarifies the signal peptide being referenced. Applicants believe this is sufficient to overcome the rejection, and therefore respectfully request its withdrawal.

CONCLUSION

In view of the above amendments and remarks, reconsideration and allowance of the pending claims is believed to be warranted, and such action is respectfully requested. The

Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

An EFS Web Filing Credit Card Payment Form authorizing payment in the amount of $780.00, representing the fee for a small entity under 41.20(b)1) in the amount of $255.00 and 37 C.F.R. § 1.17(a)(3) in the amount of $525.00, a Notice of Appeal, and a Request for Extension of Time are being submitted electronically. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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/Janell T. Cleveland/ April 7, 2008
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